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| Applicant's or agent's file reference 022-2003 WO1 | Date of mailing (day/month/year) 05 August 2003 |
| International application No. PCT/DK 03/00463 | International filing date (day/month/year) 02 July 2003 |
| Applicant ZEALAND PHARMA A/S et.al. | |

1. ☒ This receiving Office hereby gives notice of the receipt of the priority document(s) identified below on:
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| Priority date | Priority application No. | Country or regional Office or PCT receiving Office |
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| 04 July 2003 | 60/393,917 | US |
| 24 April 2002 | 60/465,613 | US |

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09.11.04

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International Patent Application No. PCT/DK03/00463
Our Ref: 022-2003 WO1

Date
07 September 2004

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Dear M. van Heusden,

This is in response to your written opinion dated 7. April 2004.

Ad. 1.4 (enablement and clarity)

The present invention is concerned with the therapeutic use of GLP-1 or a related molecule in the treatment of diabetes. The invention describes how the administration of GLP-1 or a related molecule produces a so-called "drug holiday". The latter is defined on page 5, lines 4-6 as the reduction of administration of the drug over a time period, and again on page 11, lines 29-30: "a preferred drug holiday is defined as the time interval between a first endpoint (start) and a second endpoint (finish)".

The present application discloses the effects of such a "drug holiday" in example 3 on page 31. Here it is described how animals were given a daily dose of compound 1 for a period of 50 days. After the 50 days some of the animals were no longer receiving compound 1 but a vehicle, whereas others continued to receive compound 1. After 90 days the group of animals not receiving compound 1 after the 50 days period still had a

sustained effect on their glucose metabolism (figures 5-8). This experiment showed how the effect of compound 1 would persist during a drug holiday.

The examiner is questioning whether the subject matter of the present invention is enabled over the entire breadth of the scope since the effect of compound 1 is shown to last for 40 days and, as mentioned by examiner, prior art document D4 discloses an experiment in which the long-term effect of compound 2 (a GLP-1 agonist) on the oral glucose tolerance test showed that the duration of action of the compound lasted up to 18 hours. Note, however, that the experiment performed in D4 uses a single dose of 100 nmol/kg i.p., and that the experiment in D4 is entirely unrelated to the concept of a drug holiday. In fact the experiment in D4 is concerned with determining how long the effect of a single dose of compound 2 may last, and thus cannot be compared to the experiments of the present invention.

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Examiner further states that the timing of drug administration/reduction seems essential to achieving the sustained effect of the compound. In the present application on page 12, lines 11-16 it is mentioned that the length of time associated with a drug holiday will vary depending on factors, such as gender, weight, medical history, and that a drug holiday may span from one day to 25 weeks. At the same token the timing of administration of GLP-1 or a related molecule to a patient in order for endogenous insulin levels to be maintained is also dependent on the above physical factors, and may thus differ from patient to patient. Defining an absolute timing regime of administration of GLP-1 or a related compound may prove difficult considering individual physical differences between patients.

The gist of the present invention is the discovery that administration of an anti-diabetic compound does not necessarily have to take place on a daily basis, as is currently the reality for many diabetics, but may be

administered much less frequently without losing the beneficial properties
of said anti-diabetic compound.

Yours sincerely,
ZEALAND PHARMA

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